REMARKS

Claims 20-41 are pending in the subject application. Applicants have hereinabove amended claims 20, 21, 22, 25, 30 and 31 and canceled claims 34-41 without disclaimer or prejudice to pursue the subject matter of these claims in the future. Support for the amendments to these claims may be found, *inter alia*, as follows: claim 20: page 9, lines 3-13; page 10 line 29 - page 11, lines 2; page 13, lines 16-22 and page 61, lines 3-5; table 2 on page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; claim 21: page 11, lines 10-15 and page; claim 22: page 11, lines 19-22, claim 25: page 10, lines 9 - 27; page 10 line 29 - page 11, line 8, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19; claim 30: page 13, lines 3-8, page 32, lines 22-25, page 51 lines 31-35; claim 31: page 11, lines 17-22, page 13, lines 16-22; table 2, page 52, page 8, lines 23-24, page 35, lines 24-25 and page 51, lines 18-19. Applicants maintain that these amendments raise no issue of new matter. Upon entry of this amendment, claims 20-33 will be pending and under examination.

June 26, 2007 Interview

Applicants thank the Examiner for taking his time to participate in the June 26, 2007 Interview.

Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 20-41 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner stated that the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which is it most nearly connected, to make and/or use the invention. Specifically, the Examiner asserted that because claims 20, 25, and 31 included the limitation "wherein the amount of paclitaxel and C_6-ceramide are effective to induce a 50% death rate of tumor cells", these claims are limited to a specific amount of paclitaxel and a specific amount of C_6-ceramide, for which undue experimentation would

be necessary.

In response, applicants respectfully traverse the Examiner's ground of rejection. Applicants note that claims 20, 25, 30 and 31, as amended, no longer recite the "wherein the amount of (a) and (b) is effective to induce a 50% death rate", but instead amended claims 20, 30 and 31, recite, in relevant part, "wherein the amount of (a) and the amount of (b) are effective in combination to induce at least a 50% growth inhibition" and amended claim 25 recites in relevant part "wherein the amount of (a) and the amount of (b) in combination are effective to induce apoptosis".

Applicants maintain Table 2 on page 52 of the subject specification provides adequate guidance for one skilled in the art to understand that the combination of paclitaxel and C_6-ceramide results in at least 50% growth inhibition of tumor cells, thereby decreasing the size of tumors. Specifically, the results of Table 2 show that a combination of paclitaxel and C_6-ceramide produced 66% growth inhibition of tumors comprising cells from the human prostate cancer cell line LnCap, 51% growth inhibition of the tumors comprising the cells from the human prostate cancer cell line PC-3, 75% growth inhibition of the tumors comprising cells from the human pancreatic cancer cell line RWP-2, and 66% growth inhibition of tumors comprising cells from the TU138 human head and neck squamous carcinoma cell line.

In addition, Figures 10 and 11 demonstrate that tumor growth of TU138 was inhibited by the combination of paclitaxel and C_6-ceramide. Specifically, Figure 10 shows that TU138 cells treated with the combination of paclitaxel and C_6-ceramide resulted in 53.7% apoptosis after 24 hours of treatment and 84.9% after 48 hours. Figure 11 shows that the average size of tumors after five weeks of treatment with a combination of paclitaxel and C_6-ceramide is about 55mm2 while the average size of tumors after five weeks of treatment with either paclitaxel or C_6-ceramide alone is about 230mm^2 or 150 mm^2, respectively.

Applicants maintain that a person of ordinary skill in the art based on the disclosures of the applicants' specification would be able to make and/or use applicants' invention as recited in amended claims 20-33. Accordingly, applicants maintain that as amended, claims 20-33 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

In view of the remarks hereinabove, applicants maintain that the Examiner's ground of rejection has been overcome and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. § 103

A. Jayadev et al., in view of Mycek et al.

The Examiner rejected claims 20, 25, 30-31 and 34-41 under 35 U.S.C. §103(a) as allegedly being unpatentable over Jayadev et al., (J. Biol. Chem. 1995, Vol. 270, pages 2047-2052) in view of Mycek et al. (Lippincott's Illustrated Review: Pharmacology 2nd Edition, 1997, pages 376 and 390-392). The Examiner stated that the issue is whether the skilled artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Applicants' Invention:

Applicants' invention, as now recited in amended claim 20, provides a method for inhibiting growth of a tumor comprising prostate cancer cells, pancreatic cancer cells, or head and neck squamous carcinoma cells, which method comprises contacting the tumor with (a) an amount of paclitaxel, and (b) an amount of C6-ceramide, sequentially or concomitantly, wherein the amount of (a) and the amount of (b) in combination are effective to induce at least 50% growth inhibition of the tumor thereby inhibiting the growth of the tumor.

Applicants' invention also provides, as recited in amended claim 25, a method of decreasing the size of a tumor, comprising tumor cells, wherein the tumor cells are prostate cancer cells, pancreatic cancer cells, or head and neck squamous cell carcinoma cells, which method comprises contacting the tumor with (a) an amount of paclitaxel (b) an amount of C_6-ceramide, sequentially or concomitantly, wherein the amount of (a) and the amount of (b) in combination are effective to induce apoptosis of the tumor cells, and wherein the decrease in size of the tumor is greater than the decrease in size caused by contacting the tumor with either paclitaxel alone or C_6-ceramide alone, thereby decreasing the size of the tumor.

Applicants' invention further provides, as recited in amended claim 30, a pharmaceutical composition comprising paclitaxel, C_6-ceramide and a pharmaceutically acceptable carrier, wherein the amount of paclitaxel and the amount of C6-ceramide in combination are effective to induce at least a 50% growth inhibition of a tumor.

Lastly, applicants' invention provides, as recited in amended claim 31, a method for treating a subject afflicted with prostate cancer, pancreatic cancer, or head and neck squamous cell cancer, which method comprises administering to the subject an amount of paclitaxel and an amount of C_6-ceramide, sequentially or concomitantly, wherein the amount of paclitaxel and C_6-ceramide are effective in combination to induce at least a 50% growth inhibition of the cells of the cancer, thereby treating the cancer.

Jayadev et al. disclose that C_6-ceramide induces a significant block in cell cycle progression accompanied by apoptosis in Molt-4 human leukemia cells. Jayadev et al. do not disclose the use of paclitaxel, or any use of any other chemotherapeutic agent in combination with C_6-ceramide. Mycek et al. disclose paclitaxel as a chemotherapeutic agent in combination therapy with other anticancer agents, but do not disclose C_6-ceramide as a possible anticancer agent.

On page 6 of the June 6, 2007 Final Office Action, the Examiner acknowledged that applicants have shown that a combination of C_6-ceramide and paclitaxel is synergistic. The Examiner, however, also alleged that the resulting synergy is not an unexpected result. The Examiner alleged that there are three expected effects that may arise from combination therapy: 1) additive effect; 2) a synergistic effect; and 3) antagonism. The Examiner therefore concluded that the synergism demonstrated by the combination of C_6-ceramide and paclitaxel is an expected result.

Applicants respectfully disagree. Applicants note that M.P.E.P. §716.02(a)(I) states that "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue" *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). M.P.E.P. §716.02(a)(I) also states "[e]vidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)". In addition, M.P.E.P. §716.02(a)(I) states that applicants must further show that results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage" *Ex Parte The NutraSweet Co.*, 19USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).

Applicants maintain that the specification on page 52, Table 2, discloses that paclitaxel and C_6-ceramide in combination produced unexpected, synergistic results. Table 2 discloses that in human LnCap prostate cancer cell lines, paclitaxel in combination with C_6-ceramide inhibited growth of the LnCap cells by 66% as compared to only 15% and 8% with administration of each of the agents alone, respectively. Table 2 also discloses that in RWP-2 human pancreatic cell lines, paclitaxel and C_6-ceramide inhibited growth of the RWP-2 cells by 75% as compared to growth inhibition of only 2% and 6% with administration

of each of the agents alone, respectively. Table 2 further discloses further that in TU138 human head and neck squamous carcinoma cell lines, paclitaxel in combination with C_6-ceramide inhibited growth of the TU138 cells by 66% as compared to growth inhibition of only 10% and 28% with administration of each of the agents alone, respectively. Accordingly, applicants have demonstrated an effect on growth inhibition with the combination of paclitaxel and C_6-ceramide which is greater than the sum of the effect of paclitaxel and C_6-ceramide taken alone for prostate cancer cells, pancreatic cancer cells and head and neck squamous carcinoma cells. Applicants note that in the July 5, 2007 Interview Summary, the Examiner acknowledged that the results for pancreatic cancer, prostate cancer and head and neck cancer, as evidenced by Table 2, are unexpected.

In addition, applicants' maintain that unexpected results for tumor growth inhibition using a combination of paclitaxel and C_6-ceramide are also shown in Figures 5A-5H. Specifically, the combination of paclitaxel and C_6-ceramide produced unexpected, synergistic results in inducing apoptosis. Specifically, Jurkat cells treated with both paclitaxel and C_6-ceramide resulted in an increase in apoptotic cells as compared to cells treated with paclitaxel alone or C_6-ceramide alone. This increase was not merely additive, but synergistic, with the percentage of apoptotic cells treated with C_6-ceramide and paclitaxel at 25.49% after 24 hours and 66.05% after 48 hours. In contrast, the percentage of apoptotic cells treated with C_6-ceramide was 0.64% after 24 hours and 0.33% after 48 hours, and the percentage of apoptotic cells treated with paclitaxel after 24 hours was 1.16% and 19.60% after 48 hours. A person of ordinary skill in the art would recognize that the effect of paclitaxel and C_6-ceramide in inducing apoptosis is synergistic.

Applicants also maintain that neither Jayadev et al. nor Mycek et al. disclose that a combination of paclitaxel and C_6-ceramide is or would be expected to show synergistic effects on tumor growth inhibition. In fact, Jayadev et al. do not disclose any combination of C_6-ceramide

with any other chemotherapeutic agent. Mycek et al. only disclose that paclitaxel in combination with other chemotherapeutic agents is being evaluated. Neither of these references disclose any expected results of combination therapy with paclitaxel and C_6-ceramide.

Accordingly, applicants maintain these unexpected results render nonobvious the applicants' invention as recited in claims amended claims 20, 25, 30 and 31 nonobvious over Jayadev et al. in view of Mycek et al.

In view of these remarks, applicants maintain that claims 20, 25, 30-31 satisfy the requirements of 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

B. Spencer et al. in view of Cai et al.

The Examiner rejected claims 20-41 under 35 U.S.C. §103(a) as allegedly unpatentable over Spencer et al (Drugs, 1994, vol. 48, pages 794-847) in view of Cai et al (J. Biol. Chem., 1997, vol.272, pages 6918-6926). As discussed above, the Examiner asserted that the issue is whether the skill artisan would have been motivated to administer a combination of paclitaxel and C_6-ceramide to treat cancer.

In response, applicants respectfully traverse the Examiner's ground of rejection.

Spencer et al. disclose paclitaxel as an anticancer agent with broad - spectrum anticancer activity, including breast carcinoma, colon carcinoma, head and neck squamous cell carcinoma, leukemia, pancreatic carcinoma and prostate cancer. Spencer et al. further disclose combination therapy comprising paclitaxel and several other anticancer agents, but do not disclose combination therapy with C_6-ceramide. Cai et al. teach C_6-ceramide induces apoptosis in both TNF-sensitive and TNF-resistant breast cancer cells, but does not teach the combination of C_6-ceramide with paclitaxel or any other anticancer agent.

Applicants maintain that the specification on page 52, Table 2, discloses that paclitaxel and C_6-ceramide in combination produced unexpected, synergistic results. Table 2 discloses that in human LnCap prostate cancer cell lines, paclitaxel in combination with C_6-ceramide inhibited growth of the LnCap cells by 66% as compared to only 15% and 8% with administration of each of the agents alone, respectively. Table 2 also discloses that in RWP-2 human pancreatic cell lines, paclitaxel and C_6-ceramide inhibited growth of the RWP-2 cells by 75% as compared to growth inhibition of only 2% and 6% with administration of each of the agents alone, respectively. Table 2 further discloses further that in TU138 human head and neck squamous carcinoma cell lines, paclitaxel in combination with C_6-ceramide inhibited growth of the TU138 cells by 66% as compared to growth inhibition of only 10% and 28% with administration of each of the agents alone, respectively. Accordingly, applicants have demonstrated an effect on growth inhibition with the combination of paclitaxel and C_6-ceramide which is greater than the sum of the effect of paclitaxel and C_6-ceramide taken alone for prostate cancer cells, pancreatic cancer cells and head and neck squamous carcinoma cells. Applicants note that in the July 5, 2007 Interview Summary, the Examiner acknowledged that the results for pancreatic cancer, prostate cancer and head and neck cancer, as evidenced by Table 2, are unexpected.

In addition, applicants' maintain that unexpected results for tumor growth inhibition using a combination of paclitaxel and C_6-ceramide are also shown in Figures 5A-5H. Specifically, the combination of paclitaxel and C_6-ceramide produced unexpected, synergistic results in inducing apoptosis. Specifically, Jurkat cells treated with both paclitaxel and C_6-ceramide resulted in an increase in apoptotic cells as compared to cells treated with paclitaxel alone or C_6-ceramide alone. This increase was not merely additive, but synergistic, with the percentage of apoptotic cells treated with C_6-ceramide and paclitaxel at 25.49% after 24 hours and 66.05% after 48 hours. In contrast, the percentage of apoptotic cells treated with C_6-ceramide

was 0.64% after 24 hours and 0.33% after 48 hours, and the percentage of apoptotic cells treated with paclitaxel after 24 hours was 1.16% and 19.60% after 48 hours. A person of ordinary skill in the art would recognize that the effect of paclitaxel and C_6-ceramide in inducing apoptosis is synergistic.

Applicants also maintain that neither Spencer et al. nor Cai et al. disclose that a synergistic effect would be expected in inhibiting tumor growth by combination therapy of paclitaxel and C_6-ceramide. In fact, Cai et al. do not disclose any combination therapy. Spencer et al. do not disclose combination therapy of paclitaxel and any other chemotherapeutic agent for the treatment of prostate cancer or pancreatic cancer. In addition, Spencer et al. disclose combination therapy of paclitaxel with cisplatin in head and neck squamous cell carcinoma cancer which only elicited a "minor response" as disclosed on page 829, section 3.3.5. Accordingly, applicants maintain that neither Spencer et al. nor Cai et al. disclose that a synergistic effect would be expected when treating cancer wells with a combination of paclitaxel and C_6-ceramide.

Applicants maintain that these unexpected results render nonobvious the applicants' invention as recited in amended claims 20-33 over Spencer et al. in view of Cai et al.

In view of these remarks, applicants maintain that amended claims 20-33 satisfy the requirements of 35 U.S.C. §103(a). Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

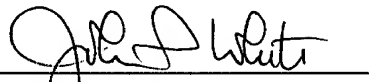
In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the June 6, 2007 Final Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection

and allow claims 20-33 as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fees, other than the $230.00 two-month extension fee and the $405.00 fee for filing a Request For Continued Examination (RCE), are deemed necessary in connection with the filing of this Amendment. Accordingly, a check in the amount of $635.00 is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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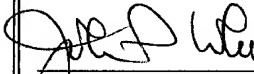

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